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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/059,720	VINSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-34,37-40,43-51,54 and 56-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-34,37-40,43-51,54 and 56-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 3/8/04 has been entered.

Amended claims 28-34, 37-40, 43-51, 54 and 56-58 are pending in the present application, with: (a) Fos protein as the elected encoded acidically modified nucleic acid binding protein, and (b) SEQ ID NO:19 as the elected amino acid sequence containing in the expressible dominant negative protein to the naturally occurring cellular protein (please note that **this is not a species election**).

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 28-34, 37-40, 43-51, 54 and 56-58 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons already set forth in the previous Office Action mailed on 12/03/03 (pages 4-7).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v.

Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

With respect to the elected invention, Applicant's invention is drawn to a transgenic non-human mammal all of whose germ cells and somatic cells, particularly adipose tissue cells, contain a recombinant acidic dominant negative polynucleotide sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, wherein the expression product of said acidic dominant negative sequence stably dimerizes or multimerizes with a normal cellular protein, for the instant case a Fos protein, and a method for producing the same. Applicants' invention is also directed to a method of creating a transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein using an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues that allows said acidically modified nucleic acid binding protein to dimerize or multimerize with the Fos protein. The claims encompass a transgenic non-human mammal having any phenotype as long as it contains a gene encoding an expressible dominant negative protein of the present invention to a Fos protein, and said dominant negative protein is expressed in cells, particularly adipose tissue cells, of said transgenic mammal; and the methods for producing the same.

Apart from the disclosure of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to

the adipose fatty acid-binding protein 422/aP2 promoter, exhibits a "skinny" phenotype, the specification fails to describe any transgenic mouse whose genome comprises a DNA sequence encoding an expressible dominant negative protein to a Fos protein (e.g., 0-hep-Fos, 1hep-Fos, 2hep-Fos or 4hepFos) having an associated desired or useful phenotype, let alone any phenotype. Nor do Applicants provide a sufficient representative number of species of a transgenic mammal or animal containing a gene encoding an expressible dominant negative protein to a Fos protein with a useful phenotype as encompassed within the scope of the presently claimed invention. Additionally, the state of the art of transgenesis at the effective filing date of the present application (5/29/1996) was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of a transgene and the result of such incorporation to cause a desired phenotype.

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure, particularly any useful phenotype associated with any transgenic non-human animal or mammal whose genome containing a gene encoding an expressible dominant negative protein to a Fos protein of the present invention, and a method for producing the same and therefore conception is not achieved until reduction to practice has occurred, regardless of the

complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Applicant's Argument

Applicant's arguments filed 3/8/04 (pages 8-9) have been fully considered but they are not persuasive.

Applicant argues that the specification describes multiple phenotypes associated with a dominant negative nucleic acid binding protein (e.g., Fos) such as decreased cell growth, suppression of neoplastic growth, decreased or inhibited foci and/or colony formation (pages 35-36, paragraph [0087]; page 37, paragraph [0090]; pages 55-58, paragraphs [0138]-[0139], in addition to the "skinny" phenotype described in Example 14 of the specification. Such phenotypes can be elicited by expression of the dominant negative nucleic acid binding protein (e.g., Fos) throughout the whole animal, or in specific tissues by way of a tissue-specific promoter. Therefore, one of ordinary skill in the art would have recognized that Applicants had possession of the claimed invention at the time the application was filed.

Please note that the cited paragraphs merely indicated that a dominant negative Fos protein of the present invention (the elected invention) is capable of inhibiting foci and/or colony formation under certain conditions *in vitro*, and that it can lead to and/or cause the suppression of neoplastic growth in a variety of cell types, especially those cells which have been growth-altered. It is apparent that these paragraphs do not indicate that at the effective filing date of the present application (5/29/1996), any useful phenotype has been made or obtained for a transgenic mouse whose genome comprises a DNA sequence encoding an expressible dominant negative protein to a Fos protein (e.g., 0-hep-Fos, 1hep-Fos, 2hep-Fos or 4hepFos). Nor do Applicants provide a sufficient representative number of species of a transgenic mammal or animal containing a gene encoding an expressible dominant negative protein to a Fos protein with a useful phenotype as encompassed by the breadth of the presently claimed invention. As already indicated above, the state of the art of transgenesis at the effective filing date of the present application (5/29/1996) was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of a transgene and the result of such incorporation to cause a desired phenotype. Particularly, the fos protein is thought to play a critical role in proliferation, differentiation in many cell types and the physiological response of mature cells to their environment; as well as its ability to interact with various Jun proteins to form AP-1 proteins which in turn interact with other transcriptional factors. To further support the unpredictability in obtaining any useful or desirable phenotype for a transgenic non-human animal whose genome comprises a DNA sequence encoding an expressible dominant negative Fos

protein of the present invention, Field et al. (Proc. Natl. Acad. Sci. 89:9306-9310, 1992) noted that despite a large body of literature suggesting an important role for c-fos in cell growth and differentiation, c-fos deficient embryonic stem cells have comparable growth rate and differentiation potential *in vitro* and *in vivo* as wild-type embryonic stem cells (see abstract). Additionally, Jain et al. (Mol. Cell. Biol. 14:1566-1574, 1994) noted that mice lacking the c-jun gene (this situation is analogous to the deficiency of functional c-jun as the result of the formation of non-functional c-jun/dominant negative c-fos heterodimers) die at midgestation; whereas c-fos deficient mice (this situation is analogous to the deficiency of functional c-fos complexes as the result of the dominant negative fos protein) are viable but show a multitude of developmental and neurological defects, but normal peripheral T-cell function (see page 1566 and abstract).

With respect to the disclosed "skinny" phenotype of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, this phenotype is irrelevant to the present elected invention (Fos protein as the elected encoded acidically modified nucleic acid binding protein). This is because the dominant negative 3heptadF C/EBP and the dominant negative Fos protein of the elected invention are structurally and biochemically distinct molecules. It should also be noted that C/EBP has been implicated in the development and differentiation of adiopose cells, and that at the effective filing date of the present application there was no evidence in the prior art or in the present disclosure that C/EBP is capable of interacting with Fos and/or Jun proteins.

Accordingly, amended claims 28-34, 37-40, 43-51, 54 and 56-58 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Amended claims 28-34, 37-40, 43-51, 54 and 56-58 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office Action mailed on 12/03/03 (pages 7-14).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, amended claims 28-34, 37 and 57 are directed to a method of creating a transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein by introducing into an embryonic cell of the non-human animal an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues, said acidic N-terminal extension allowing the acidically modified nucleic acid binding protein to dimerize or multimerize with a Fos protein.

Claims 38-40, 43-51, 54, 56 and 58 are drawn to transgenic non-human mammal whose germ cells and somatic cells contain a recombinant acidic dominant negative polynucleotide sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, wherein the expression product of said acidic dominant negative sequence stably dimerizes or multimerizes with a Fos protein, preferably the dominant negative protein is expressed adipose tissue cells of said transgenic mammal; and a method for producing the same.

Pertinent to the elected invention, the specification teaches by exemplification the preparation of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, and said transgenic mouse displays a "skinny" phenotype. The evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the presently elected invention for the following reasons.

(1) The breadth of the claims.

With respect to the elected invention, claims 28-34, 37 and 57 encompass a method of creating any transgenic non-human animal (non-human mammals as well as non-mammal animals) having any phenotype as long as it contains a gene encoding an expressible dominant negative protein to a Fos protein, via the introduction into any embryonic cell of the non-human animal an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues, said acidic N-terminal extension allowing the acidically modified nucleic acid binding protein to dimerize or multimerize with a Fos protein.

Claims 38-40, 43-51, 54, 56 and 58 are drawn to any transgenic non-human mammal having any phenotype whose germ cells and somatic cells contain a recombinant acidic dominant negative polynucleotide sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, wherein the expression product of said acidic dominant negative sequence stably dimerizes or multimerizes with a Fos protein, preferably the dominant negative protein is expressed adipose tissue cells of said transgenic mammal; and a method for producing the same.

(2) The state and the unpredictability of the art. At about the effective filing date of the present application (5/29/1996), the art of transgenesis was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of a transgene (for this instance an expressible dominant negative protein to a Fos protein) and the result of such incorporation to cause a desired phenotype in any animal species. Particularly, the predictability of an anticipated useful phenotype arises from the disruption of a particular gene or suppression the expression of a gene product. Moreadith et al. (J. Mol. Med. 75:208-216, 1997) supported phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discussed that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. reported that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (See page 208, column 2, second paragraph).

It was also known in the art that the level and specificity of a specific transgene as well as the resulting phenotype of the transgenic mouse are directly dependent on a specific transgene construct. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in a transgene construct, the specificity of transgene integration into the genome are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology 45:57-68, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph). Houdebine (J. Biotechnol. 34:269-287, 1994) also discloses that in the fields of transgenic, constructs must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (page 275, col. 1, first paragraph). Furthermore, without evidence to the contrary, transgene expression or behavior is not predictable and varies according to the particular host species, and specific promoter/gene combinations. This observation is supported by Hammer et al. (J. Anim. Sci. 63:269-278, 1986) who reported the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al. (Molecular Endocrinology 2:277-283, 1988) reported that a transgenic pig did not develop an expected phenotype of growth during the rapid growth

phase, when transfected with a Moloney murine leukemia virus rat somatotropin fusion gene (abstract, page 277). Wall et al. also stated "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 62, first paragraph).

(3) The amount of direction or guidance presented.

As enablement requires the specification to teach how to **make and use** the claimed invention, apart from the disclosure of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, displaying a "skinny" phenotype, the instant specification fails to provide any guidance for a skilled artisan on how to attain any transgenic animal or mammal whose genome comprising a gene encoding an expressible dominant negative protein to a Fos protein, and said transgenic animal or mammal has any useful phenotype. Without any disclosure for such a transgenic animal or mammal having any useful phenotype, one skilled in the art would not know how to use it and for what purposes, particularly in light of the unpredicatability for attaining a desired phenotype in the art of transgenesis as discussed above.

There is no evidence of record indicating that the expressible dominant negative 3heptadF C/EBP is also an effective dominant negative protein to the Fos protein. Baxevanis et al. (Current Opinion in Genetics and Development, 3:278-285, 1993, IDS) have noted that the exact structural rules governing the choice of dimerization partners have not yet been determined, although heterodimers are known to form between Fos

and Jun, amongst members of the ATF/CREB family, amongst members of the C/EBP family and **between members of the ATF/CREB and Fos/Jun families**, and that the successful dimerization of bZIP proteins depends upon the ability of both the individual carboxyl-terminal alpha-helices to line up in correct register with one another and generate a symmetric coiled coil (see page 280, col. 2, under the section of specificity of dimerization). Moreover, in a post-filing art Ahn et al. (Molecular and Cellular Biology, 18:967-977, 1998; IDS), it has been reported that dominant negative inhibitors constructed by fusing a designed acidic amphipathic extension onto the N-terminus of the leucine zipper of Fos, Jun, C/eBP, ATF-2 or VBP **did not block CREB DNA binding activity** (see abstract, and Figure 3).

With respect to claims 28-34, 37 and 57 encompassing a method of creating any transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein, via the introduction into any embryonic cell of the non-human animal, the instant specification is not enabled for such a method. Apart from the ES cell approach already known in the art for creating or generating a transgenic mouse, the instant specification fails to provide sufficient teachings and/or examples demonstrating that any transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein can be generated using any embryonic cell type of the non-human animal. Moreover, with respect to the breadth of the claims encompassing any transgenic non-human animal, it is also well known that the ES cell technology is generally limited to the mouse system, since at the effective filing date of the present application Moreadith et al. note that only "putative" ES cells

exist for other species (see Summary on page 214). Seamark (Reprod. Fertil. Dev. 6:653-657, 1994) also supported this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract). Likewise, Mullins et al. (J. Clin. Invest. 98:S37-S40, 1996) stated that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell has been successfully demonstrated" (column 1, first paragraph, page S38). At the effective filing date of the present application since the prior art did not provide such guidance, it is incumbent upon the instant specification to do so. In the absence of such guidance provided by the instant specification and given the unpredictability of transgenic art as already discussed above, it would have required undue experimentation for one skilled in the art to make and use the presently elected claimed invention.

With regard to the breadth of the instant claims, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues raised above, the unpredictability of the transgenic art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the instant claimed invention.

Response to Applicant's Argument

Applicant's arguments filed 3/8/04 (pages 9-11) have been fully considered but they are not persuasive.

1. Applicant argues that the instant application is not directed to a method of creating a "knockout mouse" as described by Moreadith et al., therefore the unpredictability of phenotypes obtained for knockout mice is not relevant to the presently claimed invention.

Please note that the knockout mouse art is analogous to the depletion of functional Jun proteins or functional Fos protein complexes via the action of an acidically modified dominant negative Fos protein of the presently elected invention. In both situations, selected functional molecules are depleted or made deficient in a transgenic non-human animal.

2. Applicants further argue that the specification adequately describes and enables the creation of transgene construct by describing the individual components (e.g., promoters, enhancers, other regulatory elements), expression vectors, introduction of the transgenes into cells, as well as phenotypes associated with transgene expression. Specifically, the specification describes the successful creation of a transgenic mouse in Example 14, which transgenic mouse expresses the dominant negative 3heptaF C/EBP protein.

As already noted previously, the disclosed "skinny" phenotype of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative

3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, this phenotype is irrelevant to the present elected invention (Fos protein as the elected encoded acidically modified nucleic acid binding protein). This is because the dominant negative 3heptadF C/EBP and the dominant negative Fos protein of the elected invention are structurally and biochemically distinct molecules. It should also be noted that C/EBP has been implicated in the development and differentiation of adiopose cells, and that at the effective filing date of the present application there was no evidence in the prior art or in the present disclosure that C/EBP is capable of interacting with Fos and/or Jun proteins. Moreover, given the lack of sufficient guidance provided by the present application on how to **make and use** a transgenic non-human animal or mammal whose genome comprising a gene encoding an expressible dominant negative Fos protein that has any useful phenotype, one skilled in the art would not know how to use it and for what purposes, particularly in light of the unpredictability for attaining a desired phenotype in the art of transgenesis as evidenced by the teachings of various references cited above.

3. With respect to the issue of any embryonic cell can be used to make the transgenic non-human animal of the presently claimed invention, Applicants argue that apart from the use of ES cell technology, the specification describes multiple routes of introducing the transgene into embryonic cells of the animal, including directly injecting a transgene into an embryo (e.g., example 14 showed the injection of a construct into early-stage mouse embryo). Therefore, the specification is enabling and adequate describing the creation of transgenic animals.

Please note that not any embryonic cell can be used to create a transgenic human animal. For example, would embryonic fibroblast cells be utilized for the generation of a transgenic human animal? Embryonic stem cells and early stage-embryos can be used to make transgenic animals.

4. The Declaration under 37 CFR 1.132 filed on 3/8/04 is insufficient to overcome the rejection of claims 28-34, 37-40, 43-51, 54 and 56-58 based upon insufficient disclosure under 35 U.S.C. 112, First paragraph, as set forth in the last Office action because: the present disclosure does not teach the make and use of a transgenic mouse expressing a dominant negative, acidically modified Fos molecule under the control of the tetracycline operator region (Tet-O-A-FOS), which was then crossed with the bovine Keratin 5 promoter tet-transactivator mouse (bK5-tTA) which tissue-specifically targeted expression to basal keratinocytes and out rooth sheet hair follicle cells; or the make and use of a triple transgenic mouse which results from the crossing of the double transgenic mouse (K5/A-FOS) with an AP-1 reporter transgenic line (TRE-Luciferase) to be utilized in a multiple stage skin carcinogenesis model. Applicants are invited to point out the specific page number and line number teaching these specific embodiments in the present application. It is also apparent that from the Declaration that that the A-FOS transgenic mouse has a normal phenotype as that of a wild-type mouse. Moreover, the disclosure of the A-FOS transgenic mouse is not commensurate to the broad genus of a transgenic non-human animal whose genome comprises a DNA sequence encoding an expressible dominant negative Fos protein, and the method for making the same of the presently elected invention, particularly

given the state and the unpredictability of the transgenic art at the effective filing date of the present application as already discussed above.

Accordingly, amended claims 28-34, 37-40, 43-51, 54 and 56-58 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons already set forth above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

DAVID GUZO
PRIMARY EXAMINER

Quang Nguyen, Ph.D.